Epitomes

Important Advances in Clinical Medicine

Chest Diseases

The Scientific Board of the California Medical Association presents the following inventory of items of progress in chest diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in chest diseases that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association and the summaries were prepared under its direction.

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Benefits of Hyperbaric Oxygen Therapy in Infectious Disease

HYPERBARIC OXYGEN greatly enhances the effectiveness of conventional therapy in treating necrotizing soft tissue infections, refractory osteomyelitis, and infected ischemic wounds. The mechanisms of this therapy explain its beneficial effects. Tissue oxygen tension has been found to be substantially reduced in infected tissue. Standard hyperbaric oxygen treatment increases the oxygen tension to normal or above normal in infected tissues. Tissue oxygen tensions increase with repetitive treatments. The increased oxygen tension produced by hyperbaric oxygen leads to the enhanced production of superoxide, hydrogen peroxide, and other toxic oxygen radicals.

Thereby, on strict anaerobic organisms, hyperbaric oxygen has a direct bactericidal effect through the production of toxic radicals. Anaerobic organisms are extremely sensitive to these oxygen radicals because most lack the superoxide-degrading enzyme, superoxide dismutase, and the hydrogen peroxide-degrading enzyme, catalase. In contrast to anaerobic organisms, hyperbaric oxygen has no direct effect on aerobic organisms. Hyperoxic conditions induce aerobic organisms to produce increased concentrations of superoxide dismutase. Phagocytic killing of many aerobic organisms is diminished under the hypoxic conditions found in infected tissues. The oxygen-dependent intracellular killing mechanisms of polymorphonuclear leukocytes require oxygen to rapidly kill many aerobic organisms. When the required oxygen is available in infected tissue through the use of hyperbaric oxygen, the level of polymorphonuclear leukocyte killing of aerobic organisms returns to normal or above normal. In addition, the aminoglycoside class of antibiotics does not kill well under low oxygen conditions. Hyperbaric oxygen potentiates the bactericidal effects of tobramycin and possibly other aminoglycosides.

Increased oxygen tension enhances wound healing by facilitating new collagen formation and subsequent angiogenesis. When the environment of fibroblasts has a low oxygen tension—less than 10 mm of mercury—the cells cannot sensitize collagen or migrate appropriately. Hyperbaric oxygen increases the oxygen availability to the fibroblasts and thereby facilitates new collagen formation and subsequent angiogenesis or migration of the ingrowing blood vessels. Hyperbaric oxygen, therefore, promotes faster healing in hypoxic infected wounds not only by increasing the effectiveness of the antibiotics but also by enhancing the collagen production and blood vessel migration.

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REFERENCES

Hunt TK, Zederfeldt B, Goldstick TK: Oxygen and healing. Am J Surg 1969; 118:521-525

Mader JT: Phagocytic killing and hyperbaric oxygen: Antibacterial mechanisms. Hyperbaric Oxygen Rev 1981; 2:37-49

Mader JT, Adams KR, Couch LA, et al: Potentiation of Tobramycin by hyperbaric oxygen in experimental *Pseudomonas aeruginosa* osteomyelitis (Abstr). Presented at 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1987

Mader JT, Brown GL, Guckian JC, et al: A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis 1980; 142:915-922

Airway Obstruction in Sarcoidosis

THE LUNGS are the most commonly involved organs in patients with sarcoidosis. The granulomata typically occur along lobular septa and are scattered throughout the pulmonary interstitium and alveolar walls. Bronchial or peribronchial granulomata occur frequently, and a granulomatous mass may protrude into the bronchial lumen on occasion. In the past, extensive physiologic studies, with a few exceptions, emphasized functional changes characteristic of restrictive pulmonary disease—that is, reduced static lung volumes, impaired diffusing capacity (transfer factor), and reduced pulmonary compliance. Recently, however, several studies have reassessed airway function in sarcoidosis.

In one study from Greece, airflow obstruction was noted in at least 30% of stage I patients and at least 44% of stage II patients. In another study of 123 consecutive black patients with sarcoidosis, 78 (63%) had reduced ratios of the forced expiratory volume in one second (FEV_1) to the forced vital capacity. Thus, airway obstruction is a common feature of sarcoidosis; the exact incidence of the abnormality varies, depending on racial and genetic factors.

Sarcoid granulomata protrude in the lumen of the airways and influence their function; enlarged lymph nodes may compress bronchi and produce narrowing; finally, in ad-

vanced cases, fibrosis may result in substantial distortion of the breathing tubes. Main, lobar, segmental, and subsegmental airways may all be involved. Decreased lung volumes might account for the flow reduction in many cases. In a large number of cases, however, the pathophysiologic basis of the obstruction seems to be related to bronchial hyperreactivity. Increased bronchial hyperresponsiveness was found in 50% of patients in two studies. We tested 26 patients with sarcoidosis; 18 (60%) showed a 20% or greater fall in FEV_1. It is clear that bronchial hyperreactivity occurs in patients with sarcoidosis, but we do not know why. The recent observation of increased levels of C3, C4, C5, and the anaphylatoxins C3a and C4a in alveolar macrophage supernates from patients with active sarcoidosis opens the door for further studies of the relative role of alveolar macrophage-produced mediators in bronchial hyperreactivity and airway obstruction in sarcoidosis.

Severe airflow obstruction rarely occurs in patients with sarcoidosis. In a few reported cases, bullous emphysema and hyperinflation were most likely related to destruction of the alveolar septa and honeycombing rather than pure airway obstruction. In one study in America, progressive airway obstruction was absent in most of the patients. It should be noted, however, that patient selection might be responsible for relatively better prognoses in European series than in American series.

Treatment with corticosteroids usually produces an improvement in vital capacity and FEV_1 but has a minimal effect on the low compliance and diffusing capacity. Corticosteroid therapy seems to benefit patients with bronchial sarcoidosis. Improvement is most likely achieved by suppressing the active macrophage and switching off the production of complement products and anaphylatoxins responsible for increased airway hyperreactivity and airway obstruction.

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REFERENCES

Adams JS, Gacad MA, Anders A, et al: Biochemical indicators of disordered vitamin D calcium homeostasis in sarcoidosis. Sarcoidosis 1986; 3:1-6

Argyropoulou PK, Patakas DA, Louridas GE: Airway function in stage I and stage II pulmonary sarcoidosis. Respiration 1984; 46:17-25

Bechtel JJ, Starr T III, Dantzker DR, et al: Airway hyperreactivity in patients with sarcoidosis. Am Rev Respir Dis 1981; 124:759-761

Manresa Presas F, Romero Colomer P, Rodriguez Sanchón B: Bronchial hyperreactivity in fresh stage I sarcoidosis. Ann NY Acad Sci 1986; 465:523-529

Meier-Sydow J, Rust MG, Kappos A, et al: The long-term course of airflow obstruction in obstructive variants of the fibrotic stage of sarcoidosis and of idiopathic pulmonary fibrosis. Ann NY Acad Sci 1986; 465:515-522

α_1-Protease Inhibitor Deficiency and Pulmonary Emphysema

THE PROTEASE-ANTIPROTEASE THEORY holds that emphysema results from digestion of elastin in areas of the lung subjected to a local excess of elastolytic protease or a deficiency of its inhibitor. This theory originated with two observations reported in the 1960s. One group reported the association between emphysema and a severe, genetically determined deficiency of α_1-protease inhibitor (α_1Pi). Another investigator described an animal model of emphysema resulting from the introduction of proteases into airways. Research over the past two decades supports the hypothesis. Proteases are found on elastic fibers in areas of emphysema. Cigarette smoke oxidatively inactivates α_1Pi, mobilizes excess leukocytes and their elastases to the lungs, causes syntheses of more readily degradable elastic fibers, and directly oxidizes and injures elastin.

Severe α_1Pi deficiency is found in perhaps 1% of patients with clinically significant emphysema. These patients have inherited two so-called Z genes in this highly polymorphic (more than 30 alleles have been described), autosomal codominant system. The PiZ phenotype is seen about once in every 2,000 births in populations of northern European origin. Circulating levels of α_1Pi are reduced to about 15% of those seen in the 95% of persons with the common or so-called PiM phenotype.

Normal and abnormal α_1-protease inhibitors have been synthesized through recombinant DNA and other methods. Therapeutic quantities are being prepared by plasma protein fractionation, and this product has been released as an orphan drug. Plasma levels of α_1Pi can be restored to presumably protective concentrations by weekly intravenous doses of 60 mg per kg of body weight. It is a safe agent as judged by year-long trials in a few patients.

Studies to show long-term clinical effects have not been done; indications for its use are not defined. Initiating therapy early in life is unreasonable because not all with the PiZ phenotype will have clinically significant lung disease. In end-stage disease, correcting a protease-antiprotease imbalance could not reverse severe lung damage. Clinical judgment, therefore, dictates using the drug in patients with early but definite signs of lung injury. There are theoretic reasons to implicate a protease-antiprotease imbalance in other forms of emphysema, but replacement therapy should be restricted to use in those with severe deficiency.

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REFERENCES

Janoff A: Elastases and emphysema—Current assessment of the protease-antiprotease hypotheses. Am Rev Respir Dis 1985; 132:417-433

Taylor JC, Mittman C (Eds): Pulmonary Emphysema and Proteolysis: 1986. Orlando, Fla, Academic Press, 1987

Wewers MD, Casolaro A, Sellers S, et al: Pulmonary Branch, NHLBI, α_1-Antitrypsin deficiency replacement study: Chronic augmentation of the antineutrophil elastase capacity of the lower respiratory tract of AAT-deficient individuals with weekly infusions of AAT (Abstr). Am Rev Respir Dis 1986; 133:A103

Radiologic Diagnosis—Chest Imaging

RADIOLOGIC DIAGNOSIS in chest medicine continues to be based on the "plain film," or a routine radiograph. Tomography of the mediastinum and lungs has been almost entirely replaced by computed tomography (CT). While most commonly used to screen the mediastinum for enlarged lymph nodes in the staging of lung cancer, CT is nearly ideal for distinguishing vascular structures from other structures or masses in the mediastinum. The requirement for intravenously administered contrast material is a modest limitation, though this causes all of the nonradiologic hazard of the procedure. Magnetic resonance imaging (MRI) in the chest offers less geometric resolution than CT but does not require contrast material to identify blood vessels. Though it is a new and expensive modality, MRI is already established as the safest and most versatile way to image vascular structures. It has the advantage in certain cases of forming clear images in other planes, such as sagittal and coronal, in addition to the transverse plane used by CT.

The most recently accepted technique for imaging the lungs is high-resolution CT. If the x-ray beam is narrowed to